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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,628	01/26/2004	Veronique Trochon	1002-04	9953
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EXAMINER				
MARVICH, MARIA				
ART UNIT		PAPER NUMBER		
1633				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/764,628

Applicant(s)

TROCHON ET AL.

Examiner

MARIA B. MARVICH

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 March 2008.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-24 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 13-24 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 1/26/04 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1448 or PTO-889)
Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____

DETAILED ACTION

Claims 13-24 are pending in this application. This office action is in response to an amendment filed 3/26/08.

Claim Objections

Applicant is advised that should claim 15 be found allowable, claim 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Should claim 19 be found allowable, claim 20 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Should claim 23 be found allowable, claim 24 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 16, 20 and 24 are drawn to properties that are inherent to the sequences recited in claims 15, 19 and 23. Specifically, as claims 15, 19 and 23 comprises the nucleic acid of SEQ ID NO:1, and this sequence encodes the disintegrin domain encode by SEQ ID NO:1, the disintegrin domain is inherently SEQ ID NO:2.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-24 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of direct administration to a melanoma or a pulmonary metastasis of a nucleic acid consisting of sequences encoding the disintegrin domain of metargidin, Met 1 to Gly 91 of SEQ ID NO: 1, wherein expression of SEQ ID NO:1 results in the decrease in intratumoral vessels and in inhibition of growth of the melanoma or for inhibition of the pulmonary metastases, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This is a new rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and *In re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a methods of decreasing intratumoral vessels to inhibit growth of melanoma and pulmonary metastases, treating melanoma by decreasing intratumoral vessels to inhibit growth of the melanoma and a method of treating pulmonary metastases by inhibiting the metastases by decreasing intratumoral vessels by administration of a nucleic acid comprising the polynucleotide sequence of SEQ ID NO:1. However, in order for diminution to occur, the sequence must be administered directly to the tumor as set forth below. As well, the

nucleic acid must have the ability to express SEQ ID NO:1 by insertion into an expression vector or by operable linkage to a promoter wherein the vector or promoter directs expression of SEQ ID NO:1.

The adamalysin family functions in proteolysis, adhesion, fusion and intracellular signaling (see Ruben et al, US 2002/0182702 ¶ 1042). The art teaches that there are two subfamilies of adamalysins 1) snake venom metalloproteases (SVMs) and 2) the ADAMS (proteins with a disintegrin domain and a metalloprotease domain). Multiple ADAMS have been identified including ADAM1, ADAMTS-1, fertilin (ADAM2), cryitestin (ADAM3), epididymal apical protein I, meltrin, MS2, TNF- α converting enzyme, Kusbain and metargidin (see Ruben et al, ¶ 0004). Within the ADAMS, the disintegrin domain functions to prevent integrin-mediated cell to cell and cell to matrix interactions such as plated aggregation, adhesion, migration of tumor cells or neutrophils or angiogenesis. There have been multiple propositions that members of the adamalysin family have a potential to treat a myriad of conditions such as those recited here (see Ruben et al US 2002/0165377 and Young et al (US 2003/0194797 in which the role of ADAM-22 and any other ADAM protein in inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis is proposed), but these propositions have not lead to the identification of any treatments that are viable options against diseases. The specification states that metargidin comprises AMEP (anti-angiogenic metargidin peptide) and is a human protein with multipotent function including blocking angiogenic functions of integrin $\alpha_v\beta_3$, inhibition of migration and formation of capillary structures and functions proapoptotically independent of modification of their cell cycle. The disintegrin

domain constitutes Met 420 to Gly 511 of the full-length metargidin. However, SEQ ID NO:1 does not encode all of the metargidin domain. Rather, SEQ ID NO:1 encodes the disintegrin domain of metargidin and this disintegrin domain is encoded by all of SEQ ID NO:1.

The method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. In fact, the specification teaches, "Likewise, most transgenic protein expression is mostly, though not exclusively, restricted to the injection site. Such experiments have failed to demonstrate widespread expression of transgenic proteins in the brain beyond two months". As well, Verma et al (Verma and Somia, Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery..., the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. In more advanced studies related to cancer, the art teaches "to bring about a desired therapeutic outcome. Reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle position in a tumour deposit." (Russell page 1165, col 2, ¶ 4-5).

The unpredictability of gene therapy is exacerbated in the instant case in the broad nature of the claims that are directed to simply administration of the nucleic acid. Claims 14, 18 and 22 require insertion of the sequence in an expression vector which suggests that the sequence should be expressed. It appears in claims 15, 19 and 23 that recite that the disintegrin domain be expressed. The specification is directed specifically to the analysis of AMEP, the disintegrin domain of metargidin encoded by Met 1 to Gly 91 of metargidin SEQ ID NO:1. Pages 8-9

Art Unit: 1633

describe specifically. Applicants synthesize AMEP in bacteria and demonstrate that this protein can function to inhibit adhesion of fibrinogen to vitronectin and fibronectin, inhibit endothelial cell migration, proliferation, capillary formation and stimulates proapoptosis in endothelial cells *in vitro*. *In vivo*, AMEP nucleic acid was electrotransferred to muscle of nude and C57B1/6 mice and inhibited growth of MDA-MB-231 tumor growth and formation of pulmonary metastases in syngeneic mice. Hence, it appears that the invention requires that these sequences be expressed.

The invention recites use of a broad group of means to decrease intratumoral vessels which only requires that SEQ ID NO:1 be administered. Given the unpredictability of the art with regard to nucleic acid expression absent the construct to do so and the poorly developed state of the art with regard to nucleic acid stability once administered, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Markland et al (US 5,814,609; see entire document) or Shi et al (US 20020077465; see entire document) in view of Merkulov et al (US 6,294,368; see entire document).

Merkulov isolate a protein comprising SEQ IDNO:11 (alignment below) and teaches that it is highly related to the ADAM disintegrins (see e.g. col 7, line 10-26). Merkulov propose administration of this molecule for treatment modalities (see e.g. bridging ¶ col 15-16).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the disintegrin domain comprising protein taught by Merklov et al in the methods taught by Markland et al and Shi et al because Merklov et al teach that it is within the ordinary skill of the art to use SEQ IDNO:4 comprising the disintegrin domain of SEQ IDNO:11 in treatment and because Markland and Shi et al teach that it is within the ordinary skill of the art to use any of a number of disintegrin containing proteins in inhibiting angiogenesis to treat melanoma. As an

initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith* -- USP2d--, slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). In this case, it is obvious to combine known technologies with known products for predictable results and Markland and Shi et al teach that it is known to administer disintegrin domains to inhibit vascularization in order to treat melanoma and Merklov teaches a disintegrin domain to be used in treatment modalities. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Weitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Art Unit: 1633

Maria B Marvich, PhD

Examiner

Art Unit 1633

/Maria B Marvich, PhD/

Primary Examiner, Art Unit 1633